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Outcomes of multidrug resistant tuberculosis treatment among human immunodeficiency virus co-infected patients taking anti-retroviral treatment at Sizwe Tropical Disease Hospital Johannesburg, South Africa

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Background: Multidrug resistant-tuberculosis (MDR-TB) is a threat to global tuberculosis control which is worsened by human immune-deficiency virus (HIV) co-infection. There is however paucity of data on the effects of antiretroviral treatment (ART) before or after starting MDR-TB treatment. This study determined predictors of mortality and treatment failure among MDR-TB-HIV co-infected patients on ART.

Methods & Materials: A retrospective medical record review of 1200 HIV co-infected MDR-TB patients admitted at Sizwe Tropical Disease Hospital, Johannesburg from 2007 to 2010 was performed. Chi-square test was used to determine treatment outcomes in MDR-TB-HIV co-infected patients on ART. Multivariable logistic regression and Poisson models were used to determine predictors of mortality and treatment failure respectively.

Results: Mortality was higher (21.8% vs. 15.4%) among patients who started ART before initiating MDR-TB treatment (p = 0.013). Factors significantly associated with mortality included: the use of ART before starting MDR-TB treatment (OR 1.65, 95% CI 1.002-2.73), severely-underweight (OR 3.71, 95% CI 1.89-7.29) and underweight (OR 2.35, 95% CI 1.30-4.26), cavities on chest x-rays at baseline (OR 1.76, 95% CI 1.08-2.94), presence of other opportunistic infections (OR 1.80, 95% CI 1.10-2.94) and presence of other co-morbidities (OR 2.26, 95% CI 1.20-4.21). Factors predicting failure were severe anaemia (IRR (OR 4.72, 95% CI 1.47-15), other co-morbidities (OR 2.39, 95% CI 1.05-5.43) and individualised regimen at baseline (OR 2.15 95% CI 0.98-4.71).

Conclusion: High mortality among patients already on ART before initiating MDR-TB treatment is a worrisome development. Management of adverse-events, opportunistic infections and co-morbidities in these patients is important if the protective benefits of being on ART are to be maximized. There is the need to intensify intervention programmes targeted at early identification of MDR-TB, treatment initiation, drug monitoring and increasing adherence among HIV co-infected MDR-TB patients.

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Cellular iron status affects drug susceptibilities and biofilm formation of mycobacterium

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Background: Continuous and widespread usage of antitubercular drugs leading Multi-Drug Resistance (MDR) acquired by *Mycobacterium tuberculosis* (MTB) demands immediate search for novel targets and mechanisms. The ability of MTB to adapt the hostile environment is essential for its survival and confers the basis of successful infection. A crucial condition that MTB must overcome during the establishment of infection within the host is iron limitation, since iron not freely available is required by both bacteria and humans. This study aims to investigate the effect of iron deprivation on drug susceptibilities of known anti-TB drugs and biofilm formation in *Mycobacterium smegmatis*, a "surrogate of MTB."

Methods & Materials: Drug susceptibility was tested using broth microdilution to determine minimal inhibitory concentration (MIC) and spot assays under iron deprivation. Membrane permeability and passive diffusion of drugs were assessed by nitrocefin hydrolysis and EtBr efflux assays respectively. Membrane disruption was also studied with transmission electron microscopy (TEM). Biofilm formation was quantitatively measured with crystal violet (CV) dye binding.

Results: The study revealed that iron deprivation led to enhanced potency of the most commonly used first line anti-TB drugs that could be reverted upon iron supplementation. It was explored that membrane homeostasis is disrupted upon iron deprivation as revealed by enhanced membrane permeability, hypersensitivity to membrane perturbing agent leading to increased passive diffusion of drug and TEM images showing detectable differences in cell envelope architecture. It was also shown that hypoxia but not alkaline pH which mimics iron deprivation also leads to enhanced potency of anti-TB drugs. Furthermore, iron seems to be indispensable to sustain genotoxic stress suggesting its possible role in DNA repair machinery. Finally, iron deprivation also inhibits biofilm formation which is an important virulence attribute.

Conclusion: The study for the first time established a link between cellular iron, drug susceptibility and biofilm of *Mycobacterium* suggesting iron as novel determinant to combat MDR.

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